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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,356	10/12/2001	Bert Vogelstein	001107.00195	8732

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EXAMINER
SIEW, JEFFREY

ART UNIT	PAPER NUMBER
1637	8

DATE MAILED: 03/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)
	09/981,356	VOGELSTEIN ET AL.
	Examiner	Art Unit
	Jeffrey Siew	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65-108* is/are pending in the application.

4a) Of the above claim(s) *104-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *65-108* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 3 p 5 0
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

SEQUENCE COMPLIANCE

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

APPLICANT IS GIVEN THE RESPONSE PERIOD SET FORTH IN THIS OFFICE ACTION IN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

2. Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

2. This application does not contain, as a separate part of the disclosure on paper copy, a "SequenceListing" as required by 37 C.F.R. 1.821(c).

Applicant Must Provide:

An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

Election/Restrictions

3. Applicant's election without traverse of Group I in Paper No. 7 is acknowledged.

Claims 104-108 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Priority

4. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. **This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application.** If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed under 35 U.S.C. 111(a0 on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or

120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

Specification

5. Throughout the specification the degree symbol should be incorporated (see e.g. page 3 line 26).

6. Nucleotide sequences require Sequence Identifier Numbers (SEQ ID NO).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 66-77,89-103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 98 & 99 are indefinite because the term "the first detectable probe" lacks antecedent basis. It is unclear as to what first detectable probe is being referred to.

B) Claims 100 & 101 are indefinite because the term "the second detectable probe" lacks antecedent basis. It is unclear as to what second detectable probe is being referred to.

C) Claim 102 is indefinite because the term "said dividing step" lacks antecedent basis in alternative parent claim 65. It is unclear as to what first detectable probe is being referred to.

D) The term "X%" renders claims 66,68-77,89-103 indefinite. It is unclear as to what range the term would encompass.

E) The term "the single target nucleic acid" in the second step of claim 67 renders the claim indefinite because it is unclear as to whether the dividing in dividing the preceding step results in a single target nucleic acid in a sample or refers to any single target within the sample. It cannot be determined as to whether the phrase refers to some specific instance of single target nucleic acid. Amendment of the claim to clarify the indefiniteness is required.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 66-73,76-78,91,102 & 103 are rejected under 35 U.S.C. 102(b) as being anticipated by Bunn et al (US5,213,961 May 25, 1993).

Bunn et al teach a method of quantifying RNA and DNA by polymerase chain reaction. They teach dividing samples by dilution such that target is less than 20% relative to non target, or at some X% ratio of target to non target or at least five fold non target to target, then amplifying and detecting product (see whole document esp. col. 4 lines 20-26: "target template and competitive templates"; col. 7 lines 10-15: 1 pg of target cDNA from 1ng of total mRNA"; col. 8 lines 25-30: "diluting DNA across log increments"; Example 2,Figures 2 & 3 "describe the ratio of gGM competitive template is in greater concentration than target cGM concentration of 0.62ng, and Figure 3b demonstrate that certain samples of 13 dilutions do not lead to

amplification product". They teach that the assay is used for detecting somatic cell mutations (see col. 9 line 67). They teach the RT-PCR of RNA to form target cDNA (col.14 lines 15-45).

The claims read broadly on a dilution scheme in which low levels of target nucleic acid are detected by PCR as in Bunn et al's teachings.

9. Claims 66-71,90,91-93 & 103 are rejected under 35 U.S.C. 102(b) as being anticipated by Kramer et al (WO99/131113 18 March 1999).

Kramer et al teach a method of quantifying DNA by polymerase chain reaction by dividing samples by dilution such that target is less than 20% relative to non target, or at some X% ratio of target to non target or at least five fold non target to target, then amplifying and detecting product (see whole document esp. page 18 & 19 "separating different tube s of PCR for amplification in Figures 3 & 4; page 10-11: co amplification of wild type and mutant nucleic acids and detection of as little as 2% mutant DNA in an otherwise wild type DNA population; page 9 lines 5-20 molecular bean probes – one specific for target and the other probe specific for co amplified non target).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 75 & 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bunn et al (US5,213,961 May 25, 1993) or Kramer et al (WO99/131113 18 March 1999) either in view of Gruenert et al (US 5,804,383 Sept 8, 1998).

The teachings of Bunn et al and Kramer et al are described previously.

Neither Bunn et al or Kramer et al teach target with base mutations or genomic DNA.

Gruenert et al teach genomic DNA amplification to detect such base mutations as in cystic fibrosis gene in sand sickle cell anemia (see col. 7 line 12 & line 56).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Gruenert et al's teachings of genomic DNA amplification to detect base mutations to either Bunn et al or Kramer et al's quantification assay in order to diagnoses and assess gene expression during gene therapies. Gruenert et al teach that amplification assays detect and differentiate between expression of unmutated and wild type DNA sequences in vitro and in vivo in which to assess gene therapies (see abstract). It would have been prima facie obvious to combine either Bunn et al's and Kramer et al's detection/quantification PCR methods

to Gruneert et al's teachings of amplification of genomic DNA to detect disease genes in order to quantify the gene expression during the gene therapy.

11. Claims 96 & 97 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bunn et al (US5,213,961 May 25, 1993) or Kramer et al (WO99/131113 18 March 1999) either in view of Sidransky (US6,291,163 Sept 18, 2001)

The teachings of Bunn et al and Kramer et al are described previously.

Neither Bunn et al or Kramer et al teach target with allelic imbalance.

Sidranksy et al teach the detection of allelic imbalance which is part of neoplastic progression (see abstract col. 3 lines 60-64, col. 4 lines 7-10).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Sidransky et al's teachings of detecting allelic imbalances to either Bunn et al or Kramer et al's quantification assay in order to diagnose neoplastic progression and lesions. It would have been prima facie obvious to combine either Bunn et al's and Kramer et al's detection/quantification PCR methods to Gruneert et al's teachings of allelic imbalances in order to detect the progression of cancer in a subject.

12. Claim 89 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bunn et al (US5,213,961 May 25, 1993) or Kramer et al (WO99/131113 18 March 1999) either in view of Schmitt et al (Forensic Science International vol. 66 pp. 129-141 1994)

The teachings of Bunn et al and Kramer et al are described previously.

Neither Bunn et al or Kramer et al teach sample is blood.

Schmitt et al teach PCR from blood samples (see abstract & page 131).

One of ordinary skill in the art would have been motivated to apply Schmitt et al's teachings of amplifying blood samples to Bunn et al or Kramer et al's PCR quantification technique in order to detect forensic samples from bloodstains. PCR amplification on blood samples, stool and lymph nodes was well known and commonly practiced in the art at the time of the invention. It would have been prima facie obvious to apply Schmitt et al's teaching of blood samples to Bunn et al and Kramer et al's amplification technique in order to amplify forensic samples for identification.

13. Claims 79-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bunn et al (US5,213,961 May 25, 1993) or Kramer et al (WO99/131113 18 March 1999) either in view of Livak et al (US5,736,333 April. 7, 1998).

The teachings of Bunn et al and Kramer et al are described previously.

Neither Bunn et al or Kramer et al teach assaying high multiple samples.

Livak et al teach the high throughput PCR analysis with multiple samples such as 864 PCR plates (see col.1 line 41).

One of ordinary skill in the art would have been motivated to apply Livak et al's teachings of PCR high multiple sample to Bunn et al or Kramer et al's PCR technique in order to detect multiple targets simultaneously. As it was well known and commonly practiced in the art to perform multiple PCR on different samples, it would have been prima facie obvious to apply

Livak et al's teaching of high multiple samples to Bunn et al or Kramer et al's PCR detection method in order to detect many different samples simultaneously resulting in higher information throughput.

14. Claim 74 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bunn et al (US5,213,961 May 25, 1993) or Kramer et al (WO99/131113 18 March 1999) either in view of Ruano et al (PNAS vol. 87 pp. 6296-63000 Au. 1990)

The teachings of Bunn et al and Kramer et al are described previously.

Neither Bunn et al or Kramer et al teach target with base mutations or genomic DNA.

Ruano et al teach single molecule dilution (SMD) in which genomic DNA concentration is one haploid equivalent per aliquot (see whole doc. esp. pp. 6296 & Fig. 3).

One of ordinary skill would have been motivated to apply Ruano et al SMD method to Bunn et al's or Kramer et al's PCR method in order to determine actual allele concentration ratios. Ruano et al state that SMD method avoids the empirical optimization of amplification conditions and allows resolution of ambiguous arrangement of polymorphic markers by isolating into definitive haplotypes. It would have been prima facie obvious to apply Ruano et al's dilution scheme to Bunn et al's or Kramer et al's PCR method et al's method in order to accurately determine allele ratios.

15. Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bunn et al (US5,213,961 May 25, 1993) or Kramer et al (WO99/131113 18 March 1999) either in view of Murtagh (US5,518,901 May 21, 1996)

The teachings of Bunn et al and Kramer et al are described previously.

Neither Bunn et al or Kramer et al teach asymmetric PCR.

Murtagh teach asymmetric PCR using internal primers to improve assay sensitivity (see col. 2lines34-37).

One of ordinary skill would have been motivated to apply Murtagh's asymmetric PCR method to Bunn et al's or Kramer et al's PCR method in order to increase assay sensitivity. As it was well known and commonly practiced in the art to perform asymmetric PCR in order to produce single strand target which possess greater hybridization efficiency. It would have been prima facie obvious to apply Murtagh's asymmetric PCR to Bunn et al's or Kramer et al's PCR method in order to increase assay sensitivity.

SUMMARY

16. Claims 98-101 are free of the prior art but rejected under 112 second paragraph. There is no prior art that teach or suggest a molecular beacon probe that has a loop consisting of 16 base pairs and a Tm of 50-51°C with a stem consisting of CACG sequence or a probe with loop of 19-20 bp and a Tm 54-56°C with a stem consisting of CACG sequence.

The closest prior art is Tyagi et al (US5,925,517) who teach a molecular beacon which has 15 base pair loop but a Tm of approximately 40°C (Tm=[(A+T)x2C + (G+C) x4C] nd the stem is GCGAG. Tyagi et al (US6,037,130) teach molecular beacon with a stem comprising CACG (see col. 11 probe 3) but with a loop of Tm 65C (see col. 28 line 54).

CONCLUSION

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Siew whose telephone number is (703) 305-3886 and whose e-mail address is Jeffrey.Siew@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner is on flex-time schedule and can best be reached on weekdays from 6:30 a.m. to 3 p.m. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119.

Any inquiry of a general nature, matching or filed papers or relating to the status of this application or proceeding should be directed to the Tracey Johnson for Art Unit 1637 whose telephone number is (703)-305-2982.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Center numbers for Group 1600 are Voice (703) 308-3290 and Before Final FAX (703) 872-9306 or After Final FAX (703) 30872-9307.

March 22, 2003.

JEFFREY SIEW
PRIMARY EXAMINER
March 22, 2003